

# Supply and Dissemination of Drug Safety Management Information

Manufacturing/marketing authorization holders of drugs must collect and examine information on proper use of drugs such as information on drug efficacy, safety and quality, and supply this information to medical institutions as specified in the Law. For this purpose, drug marketing authorization holders should prepare standard operating procedures based on the provisions in the GVP ordinance and endeavor to establish a comprehensive system for the supply and dissemination of information on proper and safe use of drugs.

## 1. PACKAGE INSERTS

The most basic tool for supplying information on drugs to health professionals is package inserts, and the contents of package inserts for prescription drugs have been specified by the Pharmaceutical Affairs Law. These package inserts are public documents that pharmaceutical marketing authorization holders are obliged to prepare for the purpose of supplying to physicians, dentists and pharmacists the information necessary to assure the safety of patients administered the drug and to promote the proper use of the drug concerned based on the provisions of the Law. The Law specifies items which must be included in package inserts or containers/wrappers (package insert information), points to consider in preparing package inserts and items which are not allowed to be included in package inserts. The revised Law enacted on November 25, 2014 included the provisions that package insert information should be based on scientific knowledge and information obtained in latest literatures, etc. and that brand names and precautions for usage and handling should be noticed prior to initiation of manufacturing/marketing or amendment followed by prompt publication. It also specifies penalties for not complying with these provisions and for including false or exaggerated information in package inserts. The MHLW has also issued notifications that provide guidelines on the actual items to be included, order of their inclusion, and preparation of package inserts, as well as guidelines on the preparation of Precautions for package inserts. Important information on adverse reactions, etc. obtained and evaluated in post-marketing surveillance on product safety must be reflected in package inserts. Because of the limitations on space and the amount of information that can be presented in package inserts, manufacturers and marketing authorization holders may prepare various types of information to supplement the package inserts.

The necessity of a complete reconsideration of package inserts was pointed out in the final report of the Council on 21st Century Pharmaceuticals entitled "Proper Use of Drugs in Future Health Care and the Role of the Regulatory Authorities" in May 1993, and in the interim report of the Study Committee on Measures to Promote Appropriate Use of Drugs in July 1995. At about the same time, the Sorivudine incident involving a very severe adverse reaction caused by the interaction of this antiviral agent and an

anticancer drug occurred, and the MHW (currently MHLW), health professionals and pharmaceutical companies considered emergency measures to assure proper supply of information on drug safety, mainly related to interactions (Notification No. 999 of PAB and Notice No. 1445 of the Japan Pharmaceutical Manufacturers Association).

To cope with this problem, the MHW (currently MHLW) established three special committees on the revision of pharmaceutical package inserts, which completed their work and submitted reports in May 1996. Based on these reports, guidelines for package inserts and for Precautions were completely revised, and the following three notifications were issued in April 1997:

- (1) Guidelines for Package Inserts for Prescription Drugs (Notification No. 606 of PAB dated April 25, 1997).**
- (2) Guidelines for Package Inserts for Prescription Drugs (Notification No. 59 of the Safety Division, PAB dated April 25, 1997).**
- (3) Guidelines for Precautions for Prescription Drugs (Notification No. 607 of PAB dated April 25, 1997).**

The main points in these notifications are as follows:

- Package inserts have been revised to make them easier to understand and to use by health professionals.
- The purpose is to supply scientifically accurate information.

Two notifications concerning package inserts for biological products were issued in May 2003: "Entries in Package Inserts for Biological Products" (Notification No. 0515005 of the PMSB dated May 15, 2003) and "the Guidelines for Entries in Package Inserts of Biological Products" (Notification No. 0520004 of the Safety Division, PMSB dated May 20, 2003). These notifications came into effect from July 2003.

Labeling was changed with the amendment of the Law in April 2005. "Manufacturer and importer" was changed to "marketing authorization holder" (Notification No. 0331008 of the Compliance and Narcotics Division, PFSB dated March 31, 2005, "Handling of Labeling of Drugs in the Amended Pharmaceutical Affairs Law"). "Drug requiring a prescription" was changed to "prescription drug" and "Caution: Use under prescription from a physician, etc." was to be entered based on Notification No. 0210001 of the PFSB dated February 2005, "Designation of prescription drugs."

To improve the supply of information on generic drugs, Notification No. 0324006 of the Safety Division, PFSB dated March 24, 2006 was issued. This notification specifies the entry of bioequivalence study data in the "Pharmacokinetics" section of the package insert.

The notification entitled "Enforcement of The Law for Partial Amendment of the Pharmaceutical Affairs Law" (Notification No. 0806-(3) of PFSB dated August 6, 2014) specified that precautions for usage and handling (package insert information) based on the latest scientific knowledge and information should be prepared to promptly reflect essential cautions, etc. based on outcome from evaluation of safety information including adverse drug reactions collected according to the provisions in the Law

and the MHLW Ordinance on GVP. Package inserts must include the package insert information based on latest findings, nonetheless package inserts prior to amendment may be attached in the following exceptional amendment case:

- (1) When the products had already been manufactured and distributed prior to amendment of package insert information (post-marketing products),
- (2) When all of the following requirements were met:
  - i. The products are manufactured and distributed within 6 months after the amendment date (within 1 year in cases of amendment of package insert information of products requiring testing or multiple products, which cannot be manufactured and marketed promptly with the amended package insert information),
  - ii. The amended package insert information are published on the PMDA website, and
  - iii. The manufacturing/marketing authorization holder of the product may promptly notify users including physicians or pharmacists of information on amendment of package insert information.

For submission of notifications, it was specified in the "Points to consider for notification of package insert information" (Notification No. 0901-(1) of the Safety Division, PFSB dated September 1, 2014) that notifications should be submitted on the web page for notification via the PMDA website before initiation of manufacturing/marketing in cases of notifications for products to be newly manufactured/marketed including new drugs (nonetheless, when information provision to medical institutions, etc. is started prior to initiation of manufacturing/marketing, the notification should be submitted in advance preferably), or before the initiation date of information provision of the amendment or the initiation date of manufacturing/marketing of products with the amended package insert, whichever is earlier, in cases of amendment of package insert information. It was also specified that package insert information should be published on the PMDA website promptly upon submission of the notification to the PMDA. Nonetheless, when there is a certain time between the notification date and the amendment date of package insert information, publication may be made in line with the scheduled amendment date.

Of note, it is possible that information provision of the amended package insert information may be initiated upon submission of the notification to the PMDA, however it is recommended that such information is provided upon confirmation of PMDA's acceptance, because some modification may be needed when any inadequacy was found at confirmation from the PMDA (Office Communication of the Safety Division, PFSB dated September 1, 2014).

## 1.1 Guidance on the Style and Format of Package Inserts

### 1) Coordination of formats

- (1) **Items considered important must be entered close to the beginning of the package inserts.**
- (2) **"Warnings" and "Contraindications" must be entered at the beginning of the package inserts. Package inserts with "Warnings"**

**have a red bracket-shaped band printed in the right margin. The "Warnings" must be in red letters encased in red and "Contraindications" must be encased in red.**

- (3) **Overlapping entries under two or more headings should be avoided, in principle.**
- (4) **The size of the package insert should be within four A4 size pages, in principle.**

### 2) Improved contents

- (1) **The "Precautions" must follow "Indications" and "Dosage and Administration" in that order.**
- (2) **The incidence of adverse reactions must be given in numerical values with appropriate classifications whenever possible.**
- (3) **"Adverse Reactions," "Interactions" etc. must be as clearly visible as possible using tables, etc.**
- (4) **The former headings "Drug Characteristics and Development Process" and "Nonclinical Studies" have been abolished, and the required information must be supplied in a scientifically accurate manner by improvement of the information given under such headings as "Clinical Pharmacology" and "Pharmacokinetics."**

### 3) Addition of new headings

- (1) **The new heading "Conditions for Approval" has been added.**
- (2) **This heading consists of a list of the dates of entry in the NHI Reimbursement Price List, initial marketing in Japan, publication of the latest reexamination and/or reevaluation results, latest approval of (additional) indications, the international birth date, etc.**

## 1.2 Headings and Their Sequence in Package Inserts

The actual headings and the sequence in which they are entered in package inserts for prescription drugs are shown below. Refer to **Fig. 17 (Layout of a Package Insert for a Prescription Drug (with "Warning"))** for the layout.

All of the headings should be included whenever possible, but when no appropriate information is available, the heading may be omitted.

For details of the contents of the headings in package inserts, refer to the three MHW notifications mentioned above (Notifications No. 606 and 607 of the PAB and Notification No. 59 of the Safety Division, PAB) and notifications related to biological products (Notification No. 0515005 of the PMSB and Notification No. 0520004 of the Safety Division, PMSB). For changes in entries in package inserts with the enforcement of the amended Pharmaceutical Affairs Law in April 2005, refer to Notification No. 133 of the Japan Pharmaceutical Manufacturers Association (JPMA) dated March 4, 2005 and Notification No. 0324006 of the Safety Division, PFSB dated March 24, 2006 concerning supply of information on generic drugs.

\* Headings and Their Sequence in Package Inserts

- 1) **Date of preparation and/or revision(s) of the package insert**
- 2) **Standard Commodity Classification No. of**

## Japan, etc.

- Standard Commodity Classification No. of Japan (SCCJ)
  - Approval number
  - Date of listing in the National Health Insurance (NHI) Reimbursement Price List
  - Date of initial marketing in Japan
  - Date(s) of latest reexamination
  - Date(s) of latest reevaluation
  - Date(s) of latest approval of additional indication(s)
  - International birth date
  - Storage, etc. (storage, expiration date, shelf-life, etc.)
- 3) Therapeutic category
  - 4) Regulatory classification (specified biological product, biological product, poisonous substance, deleterious substance, habit-forming drug, prescription drug, etc.)
  - 5) Name(s) [brand name, non-proprietary name, Japanese Accepted Name (JAN), etc.]
    - ◆ At the beginning of the package insert  
Precautions concerning specified biological products (encased in black)
  - 6) Warning(s) (in red letters encased in red)
  - 7) Contraindications (in black letters encased in red)
    - (1) Contraindications
    - (2) Relative contraindications
  - 8) Composition and description
    - (1) Composition
    - (2) Product description
  - 9) Indication(s)
    - (1) Indication(s)
    - (2) Precautions related to Indications
  - 10) Dosage and administration
    - (1) Dosage and administration
    - (2) Precautions related to dosage and administration
  - 11) Precautions (refer to Notifications No. 606 of PAB, No. 59 of the Safety Division, PAB, No. 607 of PAB, No. 0515005 of PFSB, and No. 0520004 of the Safety Division, PMSB) (refer to Sections 1.3 and 1.5)
  - 12) Pharmacokinetics
  - 13) Clinical studies
  - 14) Clinical pharmacology
  - 15) Physicochemistry (active ingredient)
  - 16) Precautions for handling
  - 17) Conditions for approval
  - 18) Packaging
  - 19) References and reference requests
    - ◆ Information of drugs with limited administration periods
  - 20) Manufactured and/or marketed by: (name and address)

## 1.3 Precautions

Reference: Age classification for pediatric use (basic standards)

- Children: under 15 years of age
- Small children: under 7 years of age
- Infants: under 1 year of age
- Newborns (neonates): under 4 weeks of age
- Low birth weight infants (premature infants): body weight of less than 2,500 g (according to the WHO recommendation)

The Precautions are prepared voluntarily by the manufacturer of the drug concerned or under the guidance of the MHLW based on the guidelines in the MHLW notifications listed previously. Information obtained from post-marketing drug use results (clinical experience) surveys, and foreign and domestic case reports and research reports is collected and evaluated, and the Precautions are revised to incorporate the latest data as required. Revisions based on the results of reexaminations and/or reevaluations are undertaken as required.

The headings\* used in the Precautions are as follows. Refer to the following MHW notifications: (1) No. 606 of PAB, (2) No. 59 of the Safety Division, PAB and (3) No. 607 of PAB, and notifications related to biological products (Notification No. 0515005 of the PMSB and Notification No. 0520004 of the Safety Division, PMSB) for details concerning the contents of Precautions.

\* Headings used with precautions

- 1) "Warning" (in red letters and encased in red at the beginning of "Precautions")
- 2) "Contraindications" (in black letters and encased in red following "Warning" in principle. However, at the beginning of the Precautions when there is no "Warning")
  - (1) Contraindications ("This product is contraindicated in the following patients.")
  - (2) Relative contraindications ("As a general rule, this product is contraindicated in the following patients. If the use of this product is considered essential, it should be administered with care.")
- 3) Precautions related to indications (In the event of such precautions, they are entered under the heading "Precautions" following "Indications" in the package insert.)
- 4) Precautions related to dosage and administration (In the event of such precautions, they are entered under the heading "Precautions" following "Dosage and Administration" in the package insert.)
- 5) Careful administration ("This product should be administered with care to the following patients.")
- 6) Important precautions
- 7) Drug interactions
  - (1) Contraindications for coadministration ("This product should not be coadministered with the following drugs.") (in black letters and encased in red, with simple explanation provided under "Contraindications" above.)

## (2) Precautions for coadministration

The MHW issued an office communication stressing that the Drug Interaction section must be based on the most recent scientific findings [office communication dated December 25, 2000 as a supplement of Notification No. 607 of PAB, MHW].

## 8) Adverse reactions (incidence shown in numerical values whenever possible)

\* A key to the frequency of adverse reactions should be provided at the beginning.

### (1) Clinically significant adverse reactions

### (2) Other adverse reactions

## 9) Use in the elderly

## 10) Use during pregnancy, delivery, or lactation

## 11) Pediatric use (low birth weight infants, newborns, infants, small children, children)

## 12) Effects on laboratory tests

## 13) Overdosage

## 14) Precautions concerning use

15) Other precautions (toxicity obtained in animal studies requiring particular caution, etc.)

## 1.4 Labeling of Excipients

When excipients such as stabilizers, preservatives, and vehicles are used in products listed in the Japan Pharmacopoeia (JP), in the Minimum Requirements for Biological Products or in the Radiopharmaceutical Standards, the names and quantities of these excipients must be included in the relevant package inserts or on the containers or wrappers.

Since safety problems considered to be caused by excipients have appeared, the names and quantities of excipients specified in Notification No. 853 of the PAB dated October 1, 1988 must be included in the relevant package inserts or, if necessary, on the containers or wrappers of all prescription drugs since October 1988.

The labeling of excipients in non-prescription drugs is the same as that for prescription drugs based on a voluntary agreement of the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) (FPMAJ Notification No. 165 dated March 27, 1991; Office Communication of the Safety Division, PAB dated June 3, 1991).

All ingredients of both prescription and non-prescription drugs must be included in the package insert based on a voluntary agreement of the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) (FPMAJ Notification No. 170 dated March 13, 2002) because of the social responsibility to disclose as much information as possible related to drugs as life-related products. For non-prescription drugs, the names of excipients, including designated ingredients entered voluntarily, must be labeled on the outer container or the equivalent. FPMAJ Notification No. 165 was canceled by the above voluntary agreement, and the above Office Communication of the Safety Division, PAB dated June 3, 1991 was also canceled by Notification No. 0409001 of the Safety Division, PMSB dated April 9, 2002.

## 1.5 Entries for Biological Products

### Specified biological products

- 1) Regulatory classification  
Specified biological products
- 2) Name  
For genetic recombinants, "recombinant" is included immediately after the non-proprietary name
- 3) Beginning of the package insert (before the "Warning")
  - (1) Risk of spread of infections derived from raw materials can not be completely eliminated.
  - (2) Summary of safety measures undertaken to prevent spread of infection.
  - (3) Use must be kept to a minimum after careful investigation of necessity in treatment of disease.
- 4) Composition and description
  - (1) Names of ingredients among raw materials and packaging materials derived from humans or other organisms
  - (2) Names of parts of humans or other organisms among raw materials
  - (3) Name of country where blood was collected as a raw material and collection methods (donor blood or non-donor blood)
- 5) Precautions, Important Precautions  
Health professionals such as physicians must explain to persons using the drug the efficacy and safety and other measures required for proper use of the drug concerned.
- 6) Precautions for handling  
Health professionals such as physicians must record the names and addresses of persons using the drug and preserve such records in medical institutions, etc.
- 7) Other items required for proper use

### Biological products (excluding specified biological products)

- 1) Regulatory classification  
Biological product
- 2) Name  
For genetic recombinants, "recombinant" is included immediately after the non-proprietary name
- 3) Composition and description
  - (1) Names of ingredients among raw materials and packaging materials derived from humans or other organisms
  - (2) Names of parts of humans or other organisms among raw materials
  - (3) Name of country where blood was collected as a raw material and collection methods (donor blood or non-donor blood)
- 4) Other items required for proper use

## 1.6 Brand Names of Prescriptions Drugs

Principles for naming of brands of prescription drugs have been specified in Notification No. 935 of the PMSB dated September 19, 2000 to prevent medication accidents. Active measures by related companies were requested in Notification No. 0602009 of the PFSB dated

June 2, 2004. The notifications issued jointly by directors of the Evaluation and Licensing Division and the Safety Division, PFSB specified handling of brand names of prescription combination drugs and heparin preparations (injection) and labeling of solutions attached to injection (Notification No. 0922002 of the Evaluation and Licensing Division, PFSB and No. 0922002 of the Safety Division, PFSB dated September 22, 2008) and handling of brand names of insulin preparations (Notification No. 0331001 of the Evaluation and Licensing Division, PFSB dated March 31, 2012). Handling of brand names of prescription combination drugs and insulin preparations was partially amended in Notification No. 0710-(7) of the Evaluation and Licensing Division, PFSB and No. 0710-(5) of the Safety Division, PFSB dated July 10, 2014). The brand name of generic drugs is required to be a name based on the Japanese Accepted Name as directed in Notification No. 0922001 of the Evaluation and Licensing Division, PFSB dated September 22, 2005 and the brand name of biosimilar products as directed in Notification No. 0214-(1) of the Evaluation and Licensing Division, PFSB dated February 14, 2013.

For generic drugs of combination drugs, unified brand names had been discussed, and since August 2013, these have been managed in accordance with voluntary consensus that unified brand names may be retained by Japan Society of Generic Medicines as trade names and used by companies on a license basis.

The application fee for revising brand name was lowered in April 2005. The timing of brand name revision for prevention of medical accident is the time for NHI price listing twice a year. As a result, measures have been completed for a total of about 5,400 products as of the NHI price listing in September 2009.

### **1.7 Information on Package Inserts in English**

Information on package inserts in English of drugs prepared by manufacturing/marketing authorization holders in Japan is available on the following JPMA homepage.

<http://www.e-search.ne.jp/~jpr/>

## **2. INFORMATION TO SUPPLEMENT PACKAGE INSERTS**

Because of space limitations in Japanese package inserts, the following main media are also of use to provide more detailed information about pharmaceutical products.

### **2.1 Outline of Prescription Pharmaceutical Product Information**

The Outline of Prescription Pharmaceutical Product Information is prepared by the manufacturing/marketing authorization holders with the objective of providing accurate and appropriate information to health professionals to assure proper use of their drugs. The brochure is available in two types: the general outline version explaining the entire description of the product (containing information under all headings of package insert) and property-specific version (containing information

under certain headings of package insert such as clinical studies and clinical pharmacology).

This document is prepared on the basis of the Guidelines for Preparation of Outlines of Prescription Pharmaceutical Product Information published by the Japan Pharmaceutical Manufacturers Association (JPMA) in April 2009 (revised in June 2013), but the contents also follow the MHLW notification on the Guidelines for Preparation of Package Inserts. The document must also comply with the JPMA Promotion Code for Prescription Drugs.

New drugs that are approved after October 2001 are marked with a logo indicating that the drug is subject to early post-marketing phase vigilance for such a period of time as specified in labeling (refer to Chapter 4, 1. GVP).

### **2.2 Pharmaceutical Interview Forms (IF)**

Pharmaceutical Interview Forms also serve to supplement package inserts. The IF basically specifies questions to be asked by pharmacists to obtain detailed information on pharmaceutical products in interviews with pharmaceutical company medical representatives (MRs). However, in order to reduce the burden on physicians and MR, the replies (detailed information) to the questions are already entered, and the IF are supplied to health professionals as material to be used in explanations and discussions concerning the product.

The Japanese Association of Hospital Pharmacists published new preparation guidelines in April 2013, and interview forms (IF) are being prepared in the new format for new drugs approved from October 2013.

## **3. SUPPLY AND DISSEMINATION OF SAFETY MANAGEMENT INFORMATION**

For the proper use of drugs, it is important that the necessary information be supplied and disseminated in an appropriate and timely manner to health professionals.

Safety management information reported to the MHLW, etc. is evaluated by the PMDA after hearing opinions of experts. After the Committee on Safety of Drugs of the Council on Drugs and Food Sanitation approves the results, the necessary administrative measures based on the evaluation results are taken. These administrative measures include the following:

- **Discontinuation of manufacturing or marketing of drugs, and recall of products**
- **Cancellation of approval**
- **Partial changes in approved items related to indications, dosage and administration, etc.**
- **Instructions for distribution of emergency safety information**
- **Instructions for distribution of safety flash reports (so-called blue letters)**
- **Revision of Precautions**
- **Changes in designation as controlled substances such as poisons, narcotics, or prescription drugs, or changes of regulatory category**
- **Instructions to companies to perform surveillance or research**

Among these measures, extremely urgent and

important safety-related information to warn the public and healthcare professionals of safety concerns or to restrict the use of products will be distributed as emergency safety information, and information necessary for improving their precautions on safety concerns earlier than the conventional approach through package inserts revision will be distributed as safety flash reports.

In addition to emergency safety information and safety flash reports, other information including notices of revision of Precautions is also distributed, but these are the most frequently used administrative measure.

In order to facilitate efficient revision of package inserts of drugs, a "Flowchart of standard procedures related to work on package inserts of drugs" has been specified in Office Communication of the Safety Division, PFSB dated November 25, 2014. This flowchart is posted on the webpage for supply of information on drugs and medical devices.

[http://www.info.pmda.go.jp/iyaku/file/h261126-003\\_1.pdf](http://www.info.pmda.go.jp/iyaku/file/h261126-003_1.pdf)

When the PMDA considers that an investigation of safety measures is necessary as a result of screening (primary and secondary) of data collected by the PMDA, a basic time schedule in weekly units is prepared in which the PMDA first sends an inquiry to the company, the company submits its opinions, an interview advice meeting is held, a meeting of experts is convened (convened about every 5 weeks), and measures (issuing of notifications, etc.) are taken. When the company considers that it is necessary to investigate safety measures, the same type of schedule is shown starting with a revision consultation from the company, holding an interview (face-to-face) advice meeting, convening a meeting of experts, and taking measures (refer to **Fig. 18** and **Fig. 19**).

The PMDA receives applications for consultation from companies for not only revision of package inserts of individual drugs but also for promotion of proper use to prevent serious adverse drug reactions, treatment safety, and other measures to improve safety of drugs. Accurate advice and guidance are given to the companies, and this contributes not only to the improvement of the safety of individual drugs but also to improvement of the system for safety measures of the company.

Refer to the following PMDA web page for consultations on revision, etc. of package inserts applied for by companies and procedures for applications for other consultations.

<http://www.pmda.go.jp/operations/anzen/info/bunsyosou/dan.html>

Media and procedures for provision and dissemination of safety management information include the obligation to prepare SOPs by drug marketing authorization holders based on the specifications in the GVP Ordinance, and provision and dissemination of information based on these SOPs.

The main information media and information dissemination procedures are described below.

### **3.1 Distribution of Emergency Safety Information (Yellow Letters)**

#### **1) Preparation criteria**

Emergency safety information ("yellow letter") is prepared by the marketing authorization holder on the basis

of discussion with the MHLW and PMDA following an order or instruction of the MHLW, voluntary decision by the marketing authorization holder, or other requirements in cases where it is judged necessary to take the measures (2) below in for drawing people (patients) or physician's emergent and specialized attention to safety-related matters and drug-use restriction in situations (1) as listed below. Practices for disseminating such information are specified in Notification No. 1031-(1) of the Safety Division, PFSB dated October 31, 2014.

#### **(1) Situations**

- **Situations where cases of deaths, disabilities, events that may lead to death or disability, and difficult-to-treat conditions are reported by ADR reporting systems**
  - **New safety-related problems such as the occurrence of unknown serious ADRs that apparently outweigh expected therapeutic benefits**
  - **Regulatory measures taken overseas to resolve and prevent emergency and significant safety issues**
  - **Safety issues considered to remain unresolved despite the dissemination of urgent safety information ("yellow letter") or safety flash reports ("blue letter")**
- #### **(2) Measures to be implemented**
- **Creation of "warning" box or addition of "warning notice"**
  - **Creation or addition of contraindications**
  - **Revision of precautions accompanying the implementation of new safety measures (e.g., laboratory tests)**
  - **Changes in indications, dosage, method of administration, or method of use for safety-related reasons**
  - **Regulatory measures (discontinuation or suspension of marketing or cancellation of approval) for safety-related reasons, accompanying a recall of a drug**
  - **Other measures for the prevention or early detection of ADRs concerned**

#### **2) Format and content**

Emergency safety information must be prepared in the style and format specified in the guidelines, using yellow paper, etc. for easy identification of important information by the public (patients) and medical personnel.

#### **3) Methods of information dissemination**

- (1) The staff (MRs) in charge of drug information of the marketing authorization holder directly distributes the information to physicians, pharmacists, and other health professionals in medical institutions. The dissemination is required to be efficiently carried out by using multiple communication tools such as direct handout, direct mail, fax, and e-mail to achieve prompt and widespread alert for safety concerns. PMDA distributes urgent safety information, revisions to package inserts, etc. to medical personnel who have registered their e-mail address with the Agency via PMDA medi-navi.
- (2) The marketing authorization holder must transfer

safety information to medical or pharmaceutical organizations and requests them to cooperate in collecting and disseminating information through efficient communication tools such as their websites. If the marketing authorization holder knows patient groups that use the products concerned, the safety information should be distributed to such groups.

Of note, for drugs of which package insert information are subjected to be notified, manufacturing/marketing authorization holders must notify the PMDA of details of amendment in package inserts prior to publication on the website of companies or the like.

#### 4) Distribution

The distribution of emergency safety information to medical institutions must be completed within 1 month of receipt of the government order, according to the plan and method of distribution. The marketing authorization holder must submit a safety information dissemination report to the Director of the Safety Division of PFSB when distribution has been completed as specified by the office.

### 3.2 Safety Flash Report (Blue Letters)

#### 1) Preparation criteria

The safety flash report ("blue letter") is prepared by the marketing authorization holder on the basis of discussion with the MHLW and PMDA following an order or instruction from the MHLW, voluntary decision by the marketing authorization holder, or other requirements in cases where it is judged necessary to take the measures specified in Section 3.1: 1-(2) above for drawing physician's urgent and specialized attention to safety-related matters and measures necessary for optimal drug use (e.g., efficient method of notification, laboratory tests, etc.) similarly to the procedures for handling important safety information as noted above but more promptly than routine revisions of "precautions for use" with an intent to prevent the recurrence and spread of health-related harm or injury to the public. Practices for disseminating such information are specified in Notification No. 1031-(1) of the Safety Division, PFSB dated October 31, 2014.

#### 2) Format and content

Safety flash reports must be prepared in the style and format specified in the guidelines, using blue paper, etc. Information contained in the reports may be required to be arranged for the public (patients) depending on the usage in practice.

#### 3) Methods of information dissemination

- (1) The staff (MRs) in charge of the drug information of the marketing authorization holder are to efficiently distribute the information to physicians, pharmacists, and other health professionals in medical institutions by using multiple communication tools such as direct handout, direct mail, fax, and e-mail to achieve prompt and widespread alert for safety concerns. PMDA distributes safety flash reports, revisions of package inserts, etc. to medical personnel who have registered their e-mail address with the

Agency via PMDA medi-navi.

- (2) The marketing authorization holder must transfer safety information to medical or pharmaceutical organizations, as appropriate, and requests them to cooperate in collecting and disseminating information through efficient communication tools such as their journals. If the marketing authorization holder knows patient groups that use products concerned, safety information should be distributed to such groups, as appropriate.

Of note, for drugs of which package insert information are subjected to be notified, manufacturing/marketing authorization holders must notify the PMDA of details of amendment in package inserts prior to publication on the website of companies or the like.

#### 4) Distribution

The distribution of emergency safety information to medical institutions must be completed within 1 month of receipt of the government order, according to the plan and method of distribution. The marketing authorization holder must submit a safety information dissemination report to the Director of the Safety Division of PFSB when distribution has been completed as specified by the office.

### 3.3 Distribution of Information by 'Notices of Revision of Precautions'

#### 1) Preparation criteria

- (1) Cases where the Director of the Safety Division of PFSB orders or recommends revision of the Precautions or other sections of package insert based on the results of an investigation by the PMDA.
- (2) Cases where the manufacturer and marketing authorization holder voluntarily revises the Precautions (revisions are to be notified to the MHLW beforehand).

#### 2) Format and content

The paper must be not yellow or blue.

#### 3) Methods of information dissemination

In the case of 1)-(1) above, MRs of the marketing authorization holder are to promptly distribute the notices to physicians, pharmacists, and other health professionals. PMDA distributes the notices of the Director of the Safety Division, PFSB, etc. to medical personnel who have registered their e-mail address with the Agency via PMDA medi-navi.

In the case of 1)-(2) above, the notices are to be distributed to health professionals, as required, as directed in 1)-(1) above.

#### 4) Distribution

The dissemination of the notices to medical institutions must be completed as soon as possible after receipt of the notification of the the Director of the Safety Division of PFSB or the decision to make a voluntary revision. Based on the instructions of the Safety Division for 1)-(1) above, the marketing authorization holder must submit a Notice of

Change for items in the Precautions of the drug concerned to the PMDA.

### **3.4 Dissemination of Information for Drugs That Have Completed Reexamination or Reevaluation**

Once the reevaluation results and reexamination results are available, the marketing authorization holder of the drug concerned disseminated information by preparing a "Notice of Reevaluation Results" and "Notice of Reexamination Results" as required, which they distribute to medical institutions. The FPMAJ compiles all of the reevaluation results and publishes a "Notice of Prescription Drug Reevaluation Results" in the journals of the Japan Medical Association, Japan Dental Association, and Japan Pharmaceutical Association.

### **3.5 Dissemination of ADR Information by the Pharmaceuticals and Medical Devices Safety Information (Information on Adverse Reactions to Drugs)**

Among the case reports and scientific reports on adverse reactions collected from the manufacturer/marketing authorization holder, and ADR reports collected from or submitted by health professionals, the MHLW compiles commentaries and Notices of Revisions of Precautions concerning important ADRs. They are supplied in digest form as "Pharmaceuticals and Medical Devices Safety Information" to health professionals who submitted ADR reports, and also published in the media, on the PMDA Home Page (<http://www.info.pmda.go.jp/>), and in various publications such as the Journal of the Japan Medical Association and the Journal of the Japanese Association of Hospital Pharmacists. An English version is sent to WHO.

The digest was published bimonthly from June 1973 and then monthly from June 2001 (from Issue No. 167) (recently, 11 issues annually). The digest is available and regularly updated at the following website of the PMDA. <http://www.info.pmda.go.jp/>

### **3.6 Dissemination of Information by Drug Safety Update**

The Society of Japanese Pharmacopoeia and the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) have been jointly editing and publishing the Drug Safety Update (DSU), which includes information on ADRs of prescription drugs (revisions of the Precautions) under supervision of the MHLW since September 1992 (10 times per year) (published by the FPMAJ since Issue No. 128 dated April 2004). The journal is distributed by mail to medical institutions nationwide including approximately 10,000 hospitals, 90,000 clinics and 60,000 dental clinics, as well as about 50,000 pharmacies and dispensing facilities within one month after printing. The journal is available and regularly updated at the following website of the PMDA. <http://www.info.pmda.go.jp/>

### **3.7 Commentaries on "Precautions" in Package Inserts of New Drugs**

Commentaries on "Precautions" in package Inserts of new drugs are prepared by the manufacturer/marketing

authorization holder of drugs to provide the most basic safety information on new drugs. The manufacturer/marketing authorization holder must prepare easy-to-understand "commentaries" concerning the basis and contents of Precautions, and their MRs distribute the commentaries to medical institutions before new drugs are used in medical practice in order to assure proper use of new drugs.

With the revisions of the guidelines for the preparation of package inserts and Precautions in April 1997, a guide for preparation of these commentaries was issued (Notification No. 88 of the Safety Division, PAB dated June 27, 1997). Thereafter, companies started to prepare commentaries on their new drugs. New drugs that are approved after October 2001 are marked with a logo indicating that the drug is subject to early post-marketing phase vigilance for such a period of time as specified in labeling (refer to Chapter 4, 3. GVP).

## **4. ELECTRONIC INFORMATION DISSEMINATION**

The MHLW received a report from its special committee on policies to supply drug information to health professionals, etc. using the Internet, which was established in 1997, and started operation of a "Drug Information System" to supply such information via the Internet at the end of May 1999 (currently PMDA Home Page, <http://www.info.pmda.go.jp/>).

The information supplied includes information regarding the proper use of drugs, information on package inserts of prescription drugs, safety information disseminated by the MHLW, cases of suspected adverse reactions collected by the MHLW, as well as information on Yellow Letters (formally-called Dear Doctor Letters)/Blue Letters, drug guide for patients, the manual for handling disorders due to adverse drug reactions, drug approval applications, drug recalls, etc.

The marketing authorization holder is required to discuss the necessity for issuance and publication of "PMDA requests on the proper use of drugs" among official notices on the proper use of drugs, if ADRs due to drug use or those due to improper drug use do not decrease despite major revisions to labeling such as an issue or revisions of warnings and precautions. The marketing authorization holder is also required to determine the necessity of disseminating such information through print media, as appropriate.

With this system, package insert information for prescription drugs is provided in SGML (Standard Generalized Markup Language) format to facilitate downloading and processing of the information for various purposes. In addition, the MHLW provides all information in PDF (Portable Document File) format in view of the inherent convenience.

The supply of package insert information for non-prescription drugs was started from March 2007 and supply of information on drug interview forms from May 2009.

The PMDA is providing services free (via PMDA medi-navi) to distribute safety-related information such as revisions to precautions in use of drugs, which has been

placed on the Agency's homepage, to medical personnel who have registered their e-mail address with the Agency. As of the end-November 2014, approximately 110,000 reports are accessible via the navi.

## **5. PACKAGE INSERTS OF NON-PRESCRIPTION DRUGS**

The MHW established a special committee to improve package inserts of non-prescription drugs in August 1996 following the revision of the guidelines for package inserts of prescription drugs, and this group issued its report in September 1998.

The PMSB of the MHLW issued notifications on August 12, 1999 on the type and format for non-prescription drugs to define items of information to be included in the package insert, entry methods for Precautions, and information that should be included on the outer containers. The style and format of the description on the outer containers or wrappers were revised to assist the purchase of suitable drugs based on labeling and issued as a notification of PFSB on October 14, 2011. The old notification of PMSB dated August 12, 1999 was abolished accordingly. For non-prescription Chinese herbal preparations with the established approval criteria, items to be included in Precautions in package inserts, etc. were presented in Notification No. 1014-(7) of the Safety Division, PFSB and No. 1014-(8) of the Evaluation and Licensing Division, PFSB dated October 14, 2011, and partially amended in Notification No. 0327-(1) of the Safety Division, PFSB and No. 0327-(1) of the Evaluation and Licensing Division, PFSB dated March 27, 2013.

Labeling requirements of excipients of non-prescription drugs are the same as those for prescription drugs according to a voluntary agreement of the JPMA (Notification No. 165 of the JPMA dated March 27, 1991) and Office Communication of the Safety Division, PAB dated June 3, 1991. Based on a voluntary agreement of the JPMA (Notification No. 170 of the JPMA dated March 13, 2002), all ingredients must be included in package inserts by March 31, 2004 and the names of excipients including voluntarily designated ingredients must be included on the outer container (or its equivalent).

Based on this voluntary agreement, Notification No. 165 of the JPMA was canceled and the Office Communication of the Safety Division, PAB dated June 3, 1991 was canceled by Notification No. 0409001 of the Safety Division, PMSB dated April 9, 2002.

For the background of labeling of drug excipients, refer to Section 1.4 on pharmaceutical excipients.

The revised Law enacted on November 25, 2014 specified that package insert information should be based on scientific knowledge and information obtained in latest literatures, etc. as is the case for prescription drugs. Nonetheless, the exceptions for package insert information to be attached to products may be applicable also as is the case in prescription drugs (refer to 1. PACKAGE INSERTS).

## **6. PACKAGE INSERTS OF GUIDANCE-MANDATORY DRUGS**

For guidance-mandatory drugs (refer to CHAPTER 2, 3.2 Classification of Drugs), as is the case for prescription drugs, package inserts should be based on scientific knowledge and information obtained in latest literatures, etc., and brand names and precautions for usage and handling should be noticed prior to initiation of manufacturing/marketing or amendment followed by prompt publication on the PMDA website (Notification No. 0806-(3) of PFSB dated August 6, 2014).

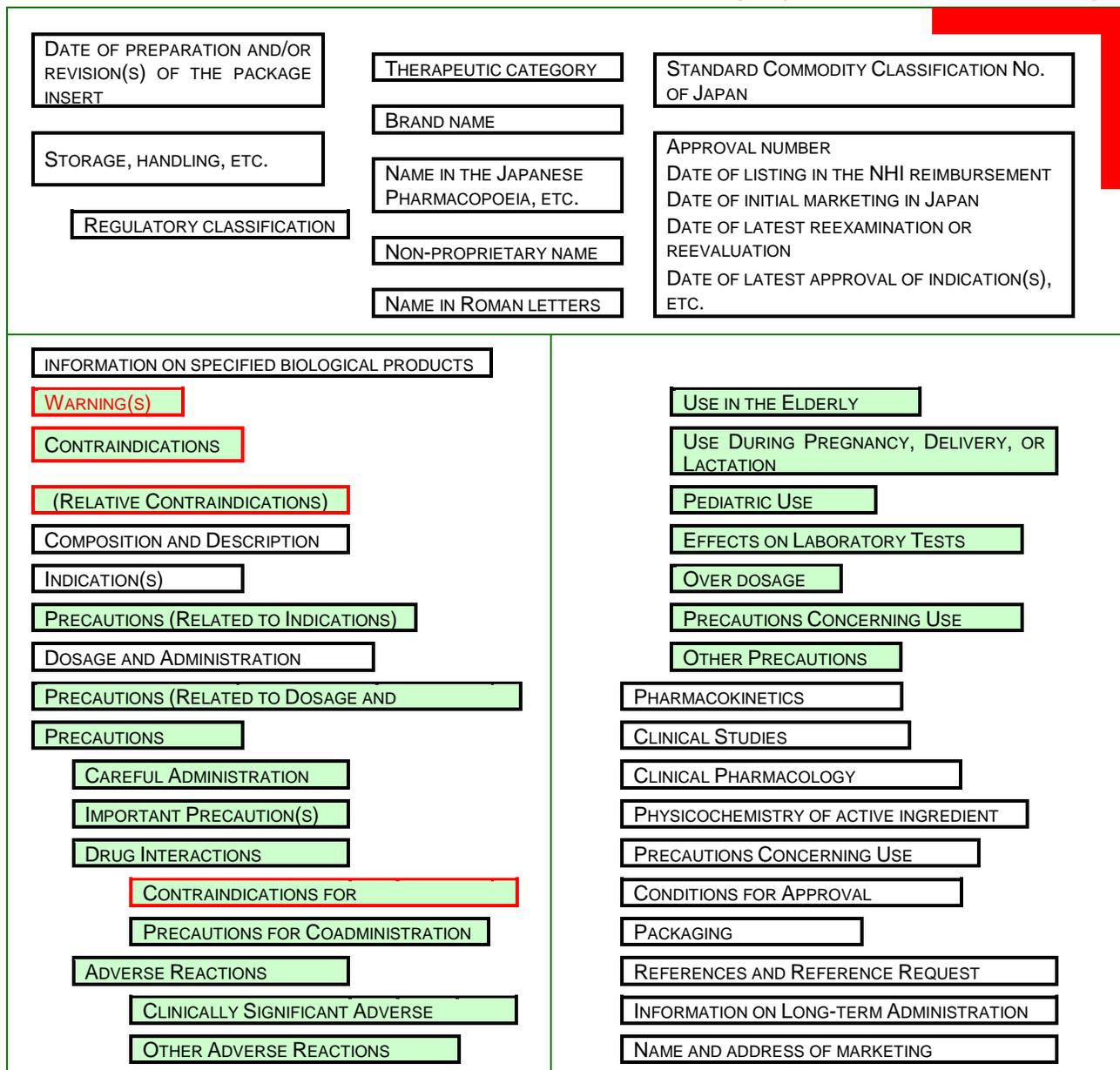
For notification, the specified notification format should be submitted to the PMDA with package insert information (copy) attached (Notification No. 0901-(1) of the Safety Division, PFSB dated September 1, 2014).

Nonetheless, the exceptions for package inserts to be attached to products may be applicable also as is the case in prescription drugs (refer to 1. PACKAGE INSERTS).

**Fig. 17 Layout of a Package Insert for a Prescription Drug (with “Warning”)**

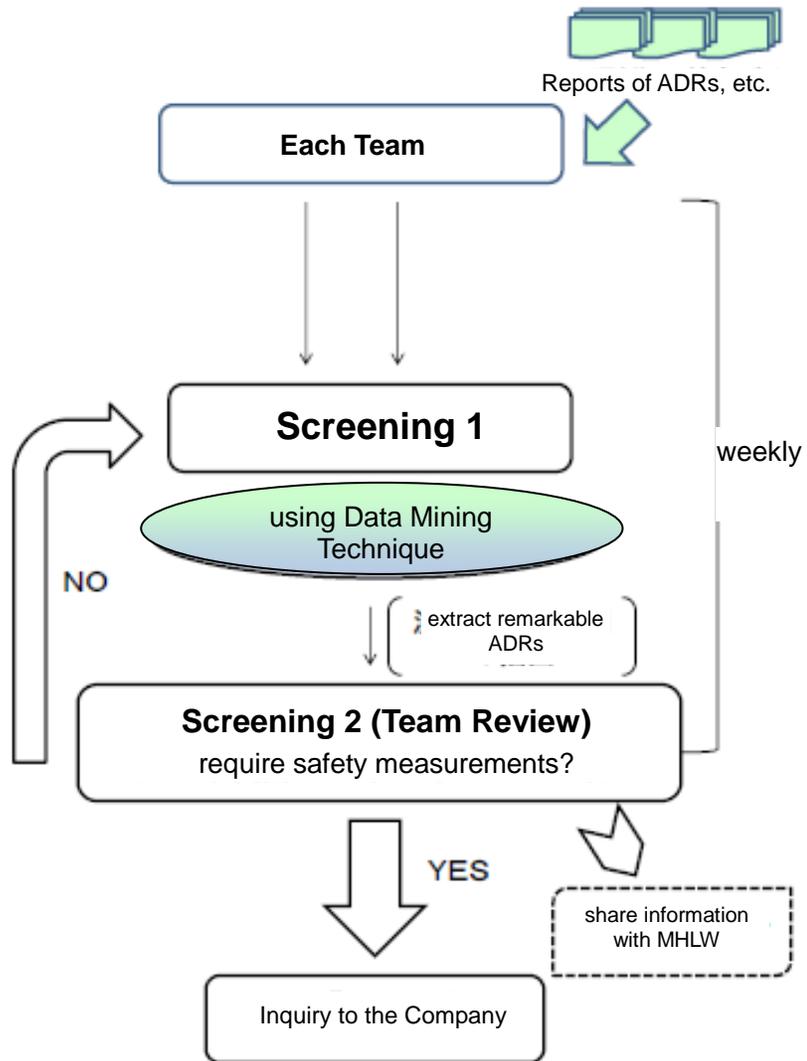
Package inserts consist of specified headings in a specified order (Refer to Chapter 5: Section 1.2). Efforts are made to carefully analyze collected information and include all headings whenever possible, but some headings are omitted when appropriate information is not available. The layout may differ to some extent.

Note: A case with “Warnings” (with a red bracket in the right margin)

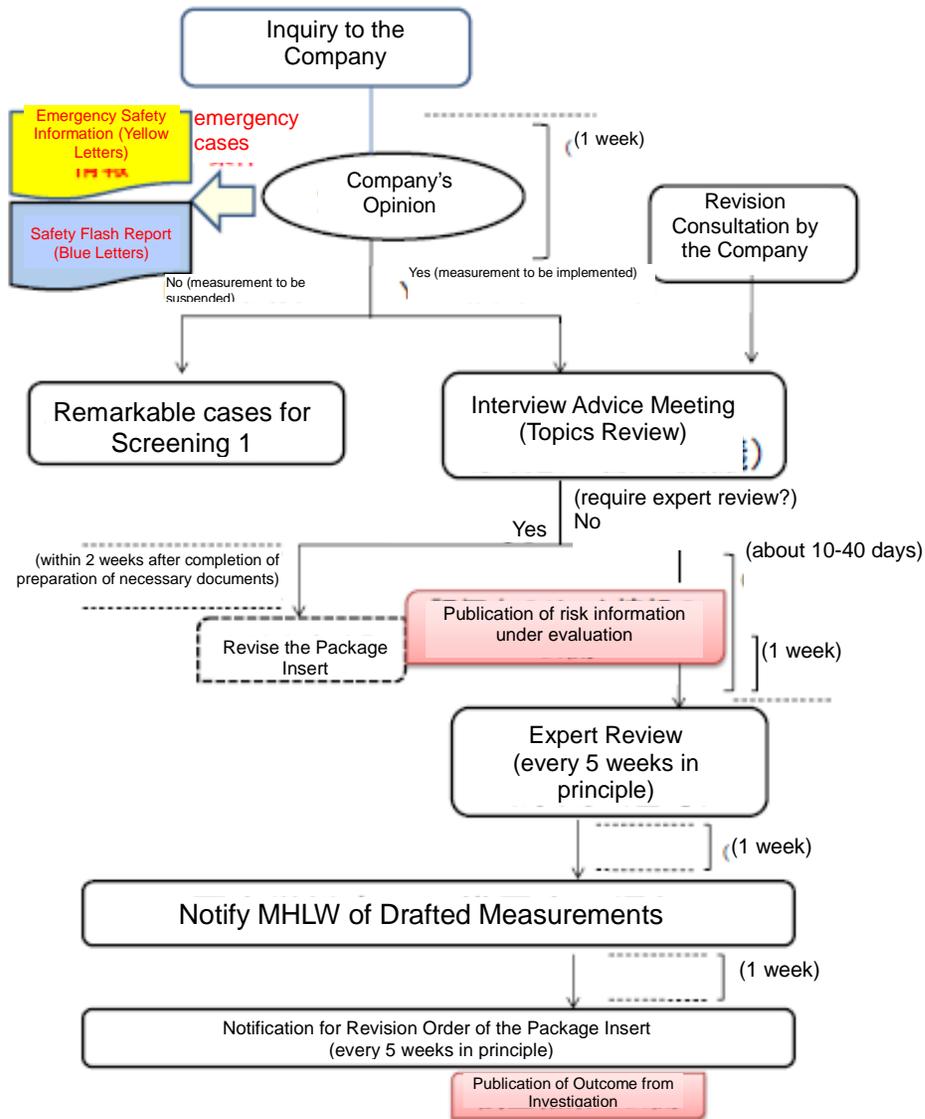


(PMS Subcommittee, Drug Evaluation Committee, JPMA)

Note: Sections in   refer to Precautions



**Fig. 18 Standard procedures for revision of package insert (1)**



**Fig. 19 Standard procedures for revision of package insert (2)**